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Efficacy and safety of high-dose chemotherapy with autologous stem cell transplantation in senior versus younger adults with newly diagnosed multiple myeloma

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Abstract

We retrospectively studied 340 fit patients with multiple myeloma (MM) who underwent autologous stem cell transplantation (ASCT). We hypothesized that progression-free survival (PFS) of older patients was non-inferior to that of younger patients after ASCT. Our null hypothesis was that the PFS hazard ratio (HR) for a 5-year increase in age was ≥1.05; the alternative (non-inferiority) hypothesis was that the HR was ≤1. The observed HR was 0.94 (95% confidence interval [CI] 0.86–1.03); since the CI upper bound was <1.05, we reject the null hypothesis and conclude that PFS in older patients was at least as good as in younger patients. We cannot reject an analogous null hypothesis for overall survival (HR 1.06 [95% CI 0.94–1.19]), since the CI upper bound >1.05. Toxicity was similar across ages and transplant-related mortality was minimal. 28% of subjects <65 versus 45% of those ≥65 received maintenance therapy. In summary, ASCT prolongs PFS equally well in older vs. younger adults. Although we cannot exclude maintenance as a confounder, these data support ASCT for fit seniors with MM.

Keywords

autologous; chemotherapy; elderly; myeloma; senior; transplantation

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1 | INTRODUCTION

Mutiple myeloma (MM) is an incurable cancer of plasma cells with an incidence that rises with age and a median age of diagnosis of 66.[1] Treatment for MM often includes high-dose chemotherapy, usually melphalan, followed by autologous stem cell transplantation (ASCT) – an approach that in both decades old and more recent studies has demonstrated the capacity to delay relapse and prolong overall survival.[2–4] Although ASCT was often not offered to senior MM subjects in the past on the basis of age alone, in more recent years the growing recognition that physiological age should supersede chronological age as a selection criterion for ASCT has resulted in increasing implementation of ASCT in seniors.[5] Multiple studies, including a large one by the Center for International Blood and Marrow Transplant Research (CIBMTR), have shown that ASCT in appropriately selected seniors is both safe and efficacious, and may also partially be responsible for improvements in survival in seniors with MM.[6–9] In the current study, our objective was to examine our own institutional experience with ASCT in seniors as compared with younger subjects with newly diagnosed MM, primarily focusing on ASCT's ability to delay MM relapse, measured as progression-free survival (PFS), but also looking at overall survival (OS) and toxicity.

2 | MATERIALS AND METHODS

We conducted a retrospective study by interrogating our database that tracks all subjects who undergo hematopoietic stem cell transplantation at our institution. Subjects were included if they underwent first ASCT between December 2000 and April 2013, and within two years of the initial MM diagnosis, and if conditioning was only with high-dose melphalan. Subjects were excluded if they were participating in other, not yet reported prospective therapy studies (i.e., embargoed data) at the time that study data were collected, if they had a separate, concurrent malignancy, or if they underwent tandem ASCT or allogeneic stem cell transplant. The study was approved by the Institutional Review Board.

Our institution reports data for all subjects undergoing stem cell transplant to CIBMTR, including these subjects. Our subjects hence represent in part a subgroup of those described in the manuscript reporting CIBMTR's experience,[6] but PFS and OS data were updated by review of the electronic health record specifically for this study. Missing OS data in the health record were determined by querying the Social Security Death Index.

Induction regimens, ASCT candidacy, stem cell mobilization regimens, melphalan dose and post-ASCT maintenance strategies were decided upon according to discretion of the treating physician. Subjects were generally mobilized and collected after receiving G-CSF (granulocyte colony stimulating factor; filgrastim), cyclophosphamide, and/or plerixafor. ASCT for MM is usually performed on an outpatient basis at our institution. On day −1, subjects received intravenous high-dose melphalan. Subjects over age 70 or younger subjects with impaired renal function (defined as a calculated creatinine clearance of <50 ml/min) were usually conditioned with dose-reduced melphalan at 140 mg/m^2, whereas other subjects generally received the standard 200 mg/m^2. On day 0, a minimum of 2×10^6 CD34$^+$ cells/kg were reinfused. Subjects received G-CSF with supportive care until engraftment.

The number of lines of induction therapy each subject received and determination of whether subject received maintenance were tabulated according to published recommendations.[10] High-risk MM was defined as the presence of any clones containing del(17p), t(4;14), 1q gain, del(1p), t(14;16) or t(14;20) by conventional cytogenetics or fluorescence *in situ* hybridization (FISH) data from any bone marrow aspirate performed prior to ASCT. All other genetic findings were considered to be standard risk. International staging system (ISS)[11] stage was determined using results obtained as close to time of diagnosis and pre-induction whenever possible. For subjects who were induced elsewhere and did not have ISS assessed prior to first evaluation at our institution, we used values obtained at their first visit with us.

Response to therapy was evaluated objectively using standard International Myeloma Working Group criteria.[12] Engraftment after ASCT was defined as transfusion-independent platelet levels ≥20,000/uL, and G-CSF-independent white blood cell count ≥1000/uL, each for at least three consecutive days. ASCT-related toxicity analyses focused on those that could be precisely determined in a retrospective chart review: unexpected hospitalization, febrile neutropenia, pneumonitis, and transplant-related mortality (TRM), defined as death not related to MM relapse within six months of ASCT.

2.1 | Statistical Considerations

The primary objective of the study was to estimate the association of age in years with PFS; secondarily, the association of age with OS was also estimated. PFS and OS were calculated from day of stem cell reinfusion. PFS was defined as time to MM progression or death, whichever came first. OS was defined as death due to any cause. Given that our primary hypothesis was that the PFS and OS of older patients receiving ASCT were similar to that of younger patients, the age effect on PFS and OS was tested under non-inferiority hypotheses. Specifically, for both PFS and OS the null hypothesis was that the HR for a 5-year increase in age was ≥ 1.05, and the alternative hypothesis was that the HR was ≤ 1. The value 1.05 is called the “non-inferiority margin” (NIM). The larger the observed HR, the larger the hazard of older patients as compared to the hazard of younger patients. While there is almost always some subjectivity in choosing a NIM, we chose a conservative NIM of 1.05 because most statisticians would consider a HR of 1.05 quite small.

The proportional hazards model was used to estimate the covariate-adjusted HR’s for the effect of age on PFS and OS. Backwards selection with a significance-level-to-stay of 0.20 was used to determine which of the candidate covariates listed in Table 1 to include in the final models, with the exception that age and year of transplant were forced into the model. The estimated hazard ratios for a 5-year increase in age are presented with 95% confidence intervals (CI). If the upper bound of the 95% CI did not include the NIM, the null hypothesis was rejected. Kaplan-Meier graphs of PFS and OS by age group (< 65 and ≥ 65) are presented for descriptive purposes. The distribution of time to engraftment, post-ASCT response status by consensus criteria,[12] neutropenia, pneumonitis, and unexpected hospitalization were estimated by age group.

3 | RESULTS

In an initial database search we identified 816 subjects and of those, 435 met the more rigorous eligibility criteria for inclusion: 11 subjects were excluded for having plasma cell cancers other than MM (e.g., light chain amyloidosis) or a concurrent malignancy separate from MM, 45 underwent allogeneic transplant or tandem ASCT, 21 were in the midst of ongoing prospective studies with embargoed data, 198 were conditioned with regimens other than melphalan monotherapy, and 106 subjects were undergoing their second or higher ASCT, or they were >2 years out from their initial MM diagnosis at the time of first ASCT. Given the critical prognostic importance of bone marrow FISH and cytogenetic results to the study's primary endpoint of PFS, we excluded another 95 subjects missing those data, resulting in 340 subjects available for the analysis. Finally, 17 patients were excluded due to missing values on other covariates.

The distribution of baseline and other relevant variables are presented in Table 1. For descriptive purposes only, age is dichotomized at age 65 (age in years was used as a continuous variable in the PFS and OS models). Most baseline and pre-ASCT characteristics were similar, including ISS stage, presence of high-risk genetics, number of induction regimens, and whether subjects received thalidomide, lenalidomide or bortezomib as part of their pre-ASCT induction therapy. The proportion of those subjects with high-risk genetics seems low, but one must consider that many of these subjects were diagnosed prior to the routine employment of FISH, and more recently CD138-enriched FISH, which has augmented the detection rate of high-risk genetic abnormalities.[13] A higher proportion of younger subjects underwent cyclophosphamide-based stem cell mobilization and full-dose (200 mg/m2) melphalan conditioning.

The distribution of ASCT response status as measured at day +100 post-ASCT is shown in Table 2. Overall response rates (i.e., achievement of PR or better) of 0.91 vs. 0.87 were observed in younger vs. senior subjects; the rates of VGPR or better were 0.58 vs. 0.65 (difference of 0.07, 95% CI, –0.05 – 0.18); the CR/sCR rates were 0.10 vs. 0.07 (difference of –0.03, 95% CI –0.13 – 0.03) (Table 2).

In the proportional hazards model of PFS, the observed HR for a 5-year increase in age was 0.94 (95% CI 0.86–1.03). Since the upper bound of the 95% CI did not include the NIM of 1.05, we concluded that the PFS of older patients was at least as good as that of younger patients. In the final PFS model, hemoglobin, cyclophosphamide-based mobilization, and pre-ASCT response independently predicted longer PFS (Table 3). Figures 1A and 2A show the distribution of PFS by age and genetic risk, respectively.

In the model of OS, the observed HR for a 5-year increase in age was 1.06 (95% CI of 0.94–1.19). Since the upper bound of 95% CI includes the NIM of 1.05, we conclude that there is no statistical evidence in this dataset that the OS of older patients was at least as good as that of younger patients. (This conclusion does not imply that the OS of older patients was significantly worse than that of younger patients. In fact, a superiority test of the association of age with OS had a p-value of 0.34.) Covariates that were retained in the OS model after backwards elimination were pre-ASCT hemoglobin, high-risk genetics, and pre-ASCT

response (Table 4). Figures 1B and 2B show the distribution of OS by age and genetic risk purely for descriptive purposes, respectively.

Median time to white blood cell engraftment was similar post-ASCT, occurring at a 12 days in subjects <65 vs. 13 days in subjects ≥65. Platelet engraftment was also similar, at a median of 13 and 14 days post-ASCT, respectively.

Toxicity, measured as the incidence of specific events, was similar between groups. Febrile neutropenia occurred in 62% and 60%, pneumonitis in 5% vs 9%, and unexpected hospitalization (a global measure of toxicity in our primarily outpatient ASCT population) in 29% and 32% of senior vs younger subjects respectively. TRM was infrequent in both groups (Table 2), and in fact, no TRM occurred in subjects above 65. Beyond that, we observed no difference in incidence of any of the toxic events analyzed between subjects who received full-vs. reduced-dose melphalan (data not shown).

Senior subjects more often received post-ASCT maintenance, usually lenalidomide: 28% of younger vs. 43% of older (difference of 0.15, 95% CI, 0.04 – 0.26) (Table 1).

4 I DISCUSSION

ASCT was one of the first therapies shown to prolong survival in MM,[2] and despite a multitude of new agents that have arrived since the advent of ASCT, most experts agree that ASCT remains a standard of care for fit subjects.[14,15] Senior adults, who were historically denied ASCT due to age alone, now undergo it far more often, supported by publications from several groups such as CIBMTR and others[6–9] that demonstrate that ASCT is safe and effective in select seniors. We now present our own data that support that contention.

In this large retrospective study we detail several key findings as relate to seniors as compared to younger MM patients: 1) ASCT is safe; 2) the PFS of seniors is as good as the PFS of younger patients; 3) this study provides no statistical evidence that would allow us to firmly state that the OS of older patients is as good as the OS of younger patients post-ASCT.

In terms of point #1, a key principle underlying our findings is the importance of appropriate subject selection and empiric modification of ASCT procedures for maximizing the safety of ASCT in seniors. We anecdotally state that our group only offers ASCT to seniors if they are fit and have limited comorbidities, although in our study we did not have data on such considerations beyond those detected on standard pre-ASCT testing. (As an example, we had data on renal function because serum creatinine is routinely checked, but no data on the presence of coronary artery disease.) In terms of modification of ASCT, our group like many others typically dose-reduces melphalan for patients >70. The similar rate of toxicity seen across ages and doses of melphalan in this study provides indirect evidence supporting the beneficial effect of these practices on patient safety. One also notes that 11% of younger subjects received dose-reduced melphalan, primarily due to renal insufficiency (data not shown).

As for points #2 and 3, PFS was as good in senior as compared to younger subjects, whereas we have no evidence to state the same for OS. PFS is a composite endpoint that includes both MM progression and death and OS includes only death as an event, so our findings suggest that ASCT delays progression in younger and older MM patients alike. Conversely, this study does not allow us to conclude that ASCT delays death equally across age groups. It does not automatically follow that post-ASCT OS is indeed worse in older adults (which would require a separate, statistical analysis for superiority), but it stands to reason that *if* OS is truly worse post-ASCT in seniors but time to MM progression is not, then the excess of deaths in seniors may be driven by factors unrelated to MM. Simply put, one's life expectancy becomes shorter as one ages due to rising likelihood of death from age-related causes, such as heart disease or other cancers.

An important confounder of PFS in our study is the fact that 15% more senior than younger subjects received maintenance. The most likely explanation for that finding is that the frequency of seniors undergoing ASCT rose with time (Table 1), as did the employment of maintenance for all MM patients. Since more seniors underwent ASCT later in the time period studied, a greater overall percentage of seniors received maintenance. Maintenance unequivocally prolongs PFS by delaying MM progression and so the potential effect of maintenance as a confounder is real.[16–18] Reassuringly, the similar ORR and depth of responses achieved both pre-ASCT and at day +100 post-ASCT, pre-maintenance, in the two age groups suggest that the benefits of ASCT are age-independent (i.e., ASCT had a similarly beneficial effect on response in both groups). That said, we ideally would have included maintenance as a time-dependent covariate in our analyses, but adequately reliable data on timing of maintenance treatments in this retrospective study were unavailable and so that analysis was not possible. We would note the fact that established predictors of outcome in MM, such as depth of response and hemoglobin, were also prognostic in this study, adding to the overall validity of our findings. Beyond that, it is somewhat surprising that cyclophosphamide-based mobilization predicted longer PFS but high-risk FISH/cytogenetics did not, whereas the converse was true for OS. Ultimately that variability probably stems from random variation in this retrospective study and/or unknown confounders that were not accounted for in multivariate modeling. The genetic analyses were also potentially confounded by the fact that FISH panels are now relatively standardized, but those assays were only evolving as routine clinical tools during much of the time frame covered by this study; it is likely that genetic abnormalities were missed in some patients.

Further limitations not yet mentioned include the fact that this is a retrospective analysis of a prospectively maintained database. Subjects were treated with a variety of induction regimens and decisions surround ASCT such as candidacy and melphalan dosing were discretionary. We attempted to circumvent that heterogeneity by controlling for relevant covariates. Another concern with all retrospective studies is that data capture is imperfect. Many subjects come to our institution for ASCT after starting induction with community physicians, and obtaining rigorous clinical data from outside practices can be challenging despite efforts to obtain outside docume. Next, the study covers more than a decade of time during which MM treatment and supportive care algorithms evolved substantially, which could also affect ASCT outcomes. We addressed that issue by controlling for year of treatment in the multivariate analysis. Lastly, we lack information on cause of death in the

majority of cases. This would be especially relevant in senior subjects, for whom competing risks of death are a very real confounder of OS. Similarly good PFS in senior vs. younger subjects post-ASCT shows that ASCT delays relapse independent of age, but ultimately showing equivalence in time to MM-related death would further support our overarching hypothesis that ASCT delays both MM relapse and MM-related death, independent of age.

Our findings parallel data from other groups:[6–9] most importantly, the PFS we observed of approximately two years is similar across all these studies, including the largest series by Sharma et al..[6] While mentioning those other studies we should highlight the uniqueness of this one: it is one of the largest single institution studies of this type and included both younger and older subjects, which enabled multivariate analysis in which age was investigated while controlling for other key covariates. This is of vital importance because multiple aspects of MM management that impact prognosis are inextricably linked to age, such as choice of induction regimen, melphalan dose, and even decisions regarding ASCT candidacy overall. Our study is also one of the most recent ones, going as far forward as 2013, whereas most other studies stopped with patients transplanted in 2011 or earlier. In the current age of rapid evolution in MM therapy, a few years can result in a sizable difference. For all these reasons, we believe our unique study adds important data to the literature in confirming the earlier findings from those older publications.

Now that we clinicians are moving beyond advanced chronological age as an absolute contraindication to ASCT, it remains to be determined how we can optimally select ASCT candidates among seniors. Several clinically relevant geriatric assessment instruments have been shown to variably predict survival and chemotherapy toxicity in the non-ASCT setting in MM[19] and in solid tumors.[20,21] Such tools could be useful in some day helping to match seniors with ideal levels of therapeutic intensity, including ASCT when appropriate, with the aim of maximizing likelihood of MM control while ensuring an acceptably low likelihood of severe toxicity. Such geriatric assessment studies are being conducted by our group and others. Very preliminary pilot studies have been completed that support feasibility,[22] but no definitive outcomes data are yet available.

Perhaps the broader, most thought-provoking question is not whether ASCT should be employed specifically in seniors with MM, but whether ASCT itself is becoming obsolete with the advent of so many new drugs including several in the United States late in 2015. Some MM experts contend that ASCT is no longer necessary. We disagree. Although it is possible that in the future ASCT may fall by the wayside, even the most recent randomized studies, which employed novel agents, still support a clear benefit for both PFS and in some studies OS when ASCT is employed as part of subjects' initial MM therapy.[3,4] We believe that ASCT remains a relevant standard of care for fit older and younger patients alike, until data may emerge which demonstrate that it is truly time to retire it.

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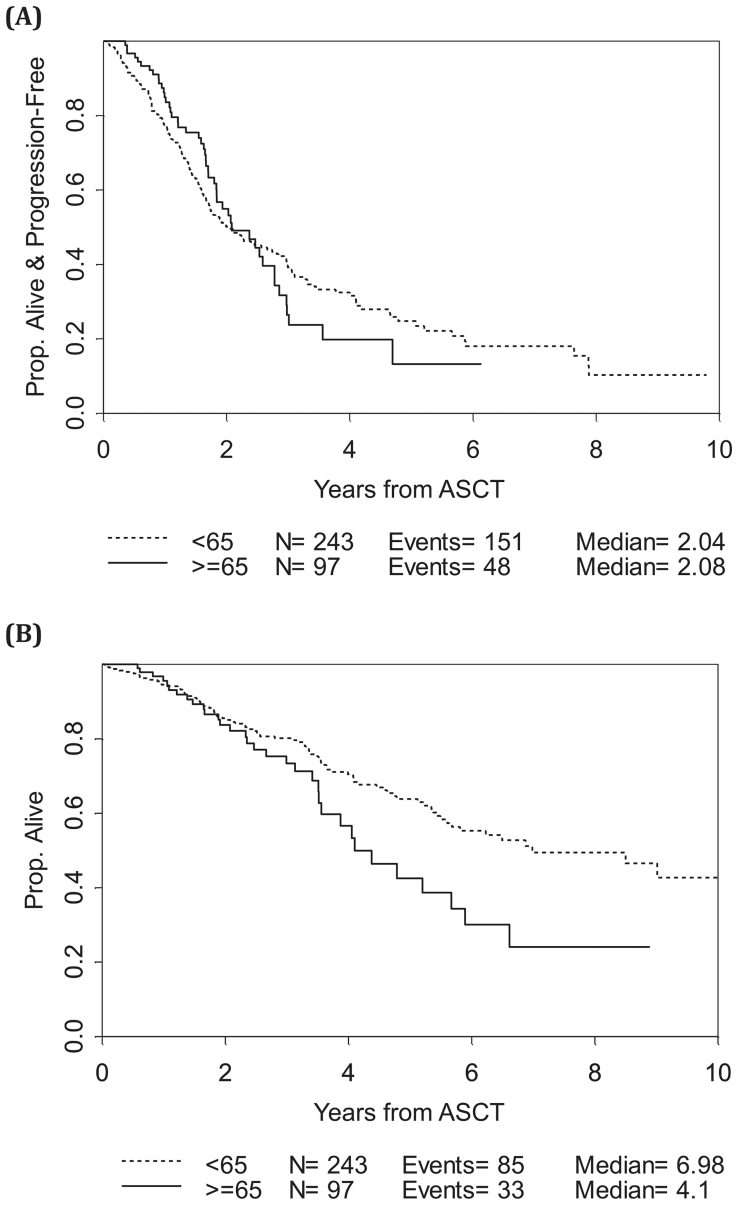

FIGURE 1. A, Progression-free survival by age. B, Overall survival by age. A and B. PFS and OS by age (figs. 1A and B respectively)

Age was statistically tested as a continuous variable, which cannot be depicted in Kaplan-Meier curves. Graphs are hence provided for illustrative purposes only

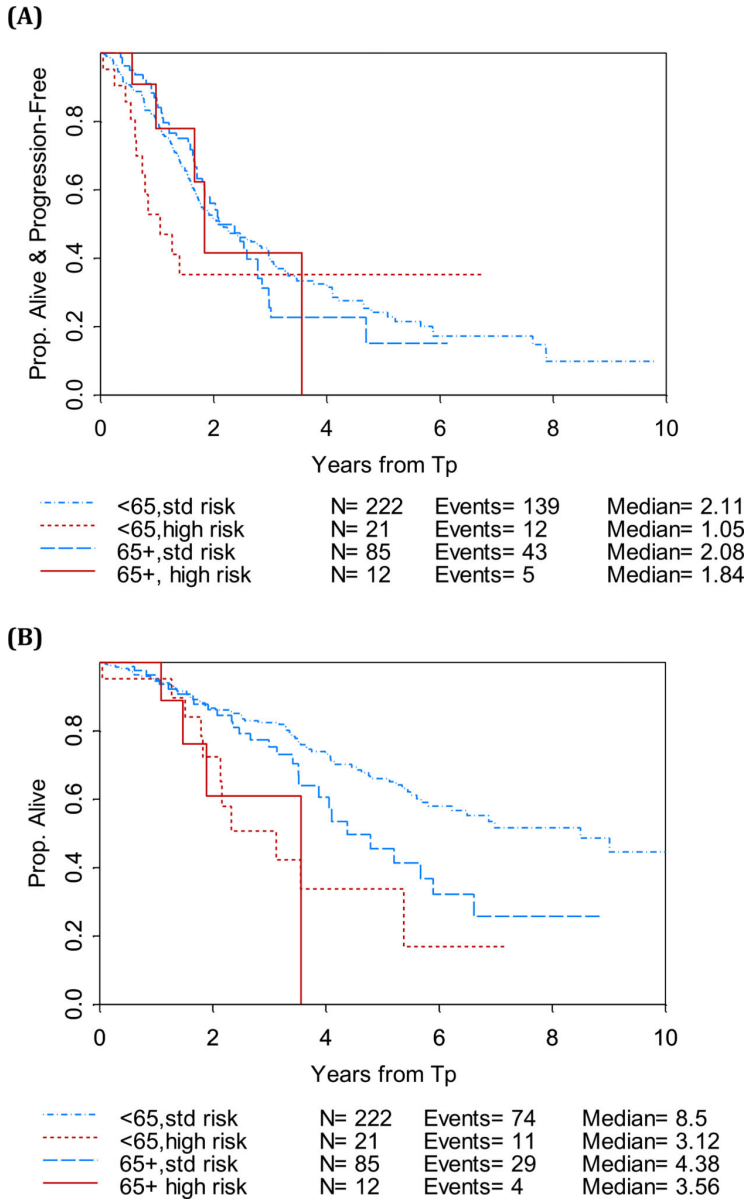

FIGURE 2. A, Progression-free survival by age, subdivided by genetic risk. B, Overall survival by age, subdivided by genetic risk. A and B. PFS and OS by age, subdivided by genetic risk

Age was statistically tested as a continuous variable, which cannot be depicted in Kaplan-Meier curves. Graphs are hence provided for illustrative purposes only

TABLE 1

Subject and disease characteristics

	Age at Transplant		
	< 65 years	≥ 65 years	Total
Characteristic	**n=243 (71%)**	**n=97 (29%)**	**N**
Median age at ASCT, (IQR)	57 (52 – 61)	68 (66 – 70)	60 (55 – 66)
Gender			
Female	109 (45%)	36 (37%)	145
Male	134 (55%)	61 (63%)	195
Immunoglobulin subtype			
IgG	142 (58%)	50 (52%)	192
IgA	50 (21%)	16 (16%)	66
IgD	1 (<1%)	1 (1%)	2
IgM	1 (<1%)	1 (1%)	2
Biclonal	0 (0%)	1 (1%)	1
Light chain	43 (18%)	26 (27%)	69
Non-secretory / unknown	6 (2%)	2 (2%)	8
FISH/cytogenetic risk			
Standard	222 (91%)	85 (88%)	307
High	21 (9%)	12 (12%)	33
ISS stage pre-ASCT			
I	146 (60%)	59 (61%)	205
II	53 (22%)	21 (22%)	74
III	30 (12%)	11 (11%)	41
Unknown / missing	14 (6%)	6 (6%)	20
Number of pre-ASCT induction regimens			
1	177 (73%)	64 (66%)	241
>1	66 (27%)	33 (34%)	99
Received thalidomide or lenalidomide pre-ASCT	141 (58%)	62 (64%)	203

	Age at Transplant		
	< 65 years	≥ 65 years	Total
Characteristic	**n=243 (71%)**	**n=97 (29%)**	**N**
Received bortezomib pre-ASCT	144 (59%)	65 (67%)	209
Median serum creatinine pre-ASCT (mg/dL), (IQR)	0.9 (0.8 – 1.2)	1.0 (0.8 – 1.2)	0.9 (0.8 – 1.2)
Median hemoglobin pre-ASCT (g/dL), (IQR)	12.1 (10.7 – 13.4)	12.0 (11.0 – 12.9)	12.1 (10.9 – 13.3)
Pre-ASCT response			
CR	28 (12%)	14 (14%)	42
sCR	4 (2%)	1 (3%)	5
VGPR	79 (33%)	24 (25%)	103
PR	108 (44%)	43 (44%)	151
SD	10 (4%)	5 (5%)	15
PD	3 (1%)	4 (4%)	7
Non-secretory/unknown	11 (5%)	6 (6%)	17
Stem cell mobilization / collection regimen			
Filgrastim only	80 (33%)	32 (33%)	112
Cyclophosphamide	132 (54%)	38 (39%)	170
Plerixafor	20 (8%)	18 (19%)	38
Cyclophosphamide + plerixafor	9 (4%)	9 (9%)	18
Marrow	1 (<1%)	0 (0%)	1
Unknown	1 (<1%)	0 (0%)	1
Melphalan dose (mg/m^2)			
<200	26 (11%)	42 (43%)	68
200	217 (89%)	55 (57%)	272
Year of transplant			
2000–2004	31 (13%)	8 (8%)	42
2005–2009	129 (53%)	26 (27%)	155
2010–2013	83 (33%)	63 (65%)	146
Post-ASCT maintenance			

	Age at Transplant		
	< 65 years	≥ 65 years	Total
Characteristic	**n=243 (71%)**	**n=97 (29%)**	**N**
Lenalidomide orthalidomide alone	56 (23%)	34 (35%)	90
Bortezomib alone	8 (3%)	4 (4%)	12
Other regimen	5 (2%)	4 (4%)	9
Any maintenance	69 (28%)	42 (43%)	111
No maintenance	174 (72%)	55 (57%)	229

IQR = interquartile range

TABLE 2

Day +100 post-ASCT MM response status

	Age at Transplant		
Response status	**< 65 years (n=243)**	**≥ 65 years (n=97)**	**Total**
sCR	3 (1%)	0 (0%)	3
CR	22 (9%)	7 (7%)	29
VGPR	117 (48%)	56 (58%)	173
PR	79 (33%)	21 (22%)	100
SD	2 (1%)	2 (2%)	4
PD	5 (2%)	4 (4%)	9
TRM	3 (1%)	0 (0%)	3
Non-secretory / unknown	12 (5%)	7 (7%)	19
Overall response rate (ORR)	**221 (91%)**	**84 (87%)**	**305**
≥VGPR	**142 (58%)**	**63 (65%)**	**205**
sCR/CR	**25 (10%)**	**7 (7%)**	**32**

TABLE 3

Multivariate analysis of progression-free survival

Variable	HR	95% CI	Significance
Age (increase of 5y)	**0.94**	**0.86 – 1.03**	**0.30** *
Year of ASCT	0.97	0.91 – 1.03	0.27
Pre-ASCT hemoglobin (increase of 1 g/dL)	0.89	0.83 – 0.96	0.0029
Thalidomide or lenalidomide with induction	1.25	0.91 – 1.72	0.18
Cyclophosphamide mobilization	0.72	0.53 – 0.97	0.030
FISH/cytogenetic high risk	1.47	0.86 – 2.50	0.16
Pre-ASCT response			
PR vs. ≥VGPR	0.48	0.35 – 0.66	<0.0001
PR vs. <PR	1.22	0.69 – 2.17	

*From test of non-inferiority

n=322; 58% events (one subject fewer than OS due to missing data)

TABLE 4

Multivariate analysis of overall survival

Variable	HR	95% CI	p-value
Age (increase of 5y)	**1.06**	**0.94 – 1.19**	**0.025** *
Year of ASCT	0.98	0.90 – 1.06	0.56
Pre-ASCT hemoglobin (increase of 1 g/dL)	0.89	0.81 – 0.98	0.019
FISH/cytogenetic high risk	2.92	1.63 – 5.23	0.0003
Pre-ASCT response			
≥VGPR	0.60	0.39 – 0.92	0.0051
<PR	1.76	0.89 – 3.50	

* From test of non-inferiority

n=323; 35% events